REMARKS

Claims 1, 3-9, 21, 23-29, 37 and 39-46 are now pending for prosecution in this case.

Response to formal objection

The Examiner has noted an inconsistency between Applicant's description of the cancelled claims between page 11, lines 1-2 and page 12, lines 11-12 in that it is unclear whether or not Applicant intended to cancel Claims 16-18. The Examiner has indicated that Claims 16-18 are presently pending, and Applicant notes for the record that despite descriptions in the Amendment of December 20, 2001 to the contrary, the actual language directing the cancellation of claims appearing on the first sentence of page 7 does not include Claims 16-18.

Responding on the merits, Applicants respectfully submit that the cancellation of Claims 16-20 renders the objection moot.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 16, 18, 9 and 29 stand rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

In response, the cancellation of Claims 16 and 18 and the amendment to Claims 9 and 29 renders the rejection moot.

The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-5, 8, 9, 16, 18, 21, 23-25, 28, 29, 37, 39 and 40 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly not being enabled by the specification to use the invention for the full scope of the claims. In particular, this rejection is maintained from the prior office action of June 20, 2001 (Paper No. 6), ostensibly because the present claims include "any or all IL-17 mediated, inflammatory cartilagenous disorders". In support of his argument, the Examiner admits that while the specification is enabling for the treatment of RA and OA with the claimed method, it provides "no evidence that such treatment is beneficial for any or all inflammatory cartilagenous disorders."

In response, Applicants respectfully submit that the claimed method is not directed to "any or all inflammatory cartilagenous disorders", but only those that are mediated by IL-17.

As the Examiner has indicated in his prior response of June 20, 2001, Applicants have taught that the specification indicates that IL-17 is able to (1) mediate a wide-range of effects, including proinflammatory and hematopoietic; (2) induce NO production in chondrocytes and is expressed in arthritic, but not normal joints; (3) induce "cartilage matrix turnover and metabolism"; (4) induce production of catabolic proteins. Moreover, the Examiner acknowledges that the specification also provides an example of an in vivo rheumatoid arthritis model and the positive effect of anti-IL-17 antibodies thereon.

Continuing, the Examiner also indicated that the prior rational for the rejection was that IL-17 appeared to be a pro-inflammatory cytokine, and that not all cartilagenous disorders appeared to be inflammatory.

The present claims relate to treatment of cartilage in an "IL-17 mediated, inflammatory cartilagenous disorder" by administration of an anti-IL-17 antibody. Applicants have provided an extraordinary level of experimental confirmation of the deleterious effects of IL-17 in *in vitro* cartilage explants as well as *in vivo* on (1) inhibition of proteoglycan (PG) synthesis, (2) stimulation of PG release, (3) additive effects of PG breakdown and reduction in PG synthesis in combination with known catabolic agents (*e.g.*, IL-1α).

Applicants have further shown that anti-IL-17 antibodies have been effective in attenuating the deleterious effects of IL-17 in an animal arthritic model (Example 4). The issue here and the claim scope is not whether the specification enable "any or all inflammatory cartilagenous disorders" as the Examiner indicates, but for an *IL-17 mediated*, inflammatory cartilagenous disorder.

The enablement requirement of 35 U.S.C. § 112, First paragraph requires that a specification describe to one of ordinary skill how to (a) *make* and (b) *use* the invention, without *undue* experimentation.

Applicants have described in extensive detail how to prepare anti-IL17 antibodies at least at page 23, line 31 through page 28, line 12 and page 41, line 33 through page 49, line 19, and the Examples. The use of these antibodies is further described at least at page 53, line 1 through page 55, line 22 and the Examples. As the Examiner has already indicated, Applicants have indeed provided experimental data relating to the treatment of cartilage in rheumatoid arthritis

using anti-IL-17 antibodies. Given the great abundance of experimental data relating to the deleterious effects of IL-17 on cartilage, it is clearly evident to anyone of any skill in the art (not just of ordinary skill) that the specification is fully enabling to a method of treating IL-17 mediated, inflammatory cartilagenous disorders with anti-IL17 antibody.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3-5, 8, 9, 21, 23-25, 28, 29, 37, 39 and 40 under 35 U.S.C. § 112, First Paragraph (Claims 16 and 18 having been cancelled).

The Rejection under 35 U.S.C. § 102(a)

Claims 1, 3-6, 8, 9, 21-26, 28, 29, 37, 39, 40 and 45 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Shigeru *et al.*, JP2000186046. The Examiner alleges that Shigeru *et al.* discloses that levels of IL-17 is significantly higher in the synovial fluids of RA patients, that anti-IL17 can inhibit osteoclastogenesis induced by IL-17 and is antirheumatic and antiarthritic and that anti-IL17 can be used to treat bone joint destruction in RA.

Shigeru *et al.* discloses that anti-IL-17 can inhibit osteoclastogenesis induction by IL-17, and as a result, might be useful in treating and preventing articular bone destruction in RA. Interestingly, Shigeru *et al.* also indicates that rheumatoid arthritis can be distinguished from osteoarthritis by the presence of IL-17. That is, IL-17 can be found in the synovial fluid and serum of rheumatoid patients, but not in those with osteoarthritis, trauma or gout - and as a result, can be used to clearly distinguish rheumatoid patients. (see page 7, para 10 and pages 12-13, para. 20).

Shigeru *et al.* does not recognize that IL-17 has a deleterious effect on cartilage. In fact, Shigeru does recognize that anti-IL17 can treat or prevent further damage to cartilage caused by IL-17. While Shigeru does recognize that anti-IL17 is potentially useful for the treatment of rheumatoid arthritis, it is strictly limited to the symptom of osteoclastogenesis (bone formation). Shigeru *et al.* does not even mention cartilage, much less disclose or suggest that anti-IL17 antibodies or even the inhibition of IL-17 might be effective in attenuating damage to cartilage. Applicants have amended the claims to specify treatment of cartilage

As a result, Shigeru does not recognize or suggest that anti-IL17 antibodies might be effective in treating or reducing damage to cartilage incident with IL-17 mediated inflammatory disorders, including rheumatoid arthritis.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3-6, 8, 9, 21-26, 28, 29, 37, 39, 40 and 45 under 35 U.S.C. § 102(a).

The First Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-6, 8, 9, 21, 23-26, 28, 29, 37, 39, 40 and 45 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chabaud *et al.*, *J. Immunol.*, 161: 409-414 (1998) in view of Carroll *et al.*, *Inflamm. Res.* 47: 1-7 (1998).

This rejection has been maintained from the initial Office Action of June 20, 2001. Essentially, the Examiner is saying that Carroll *et al.* teaches that anti-IL-6 antibody might be useful to treat rheumatoid arthritis, while Chabaud *et al.* discloses that IL-17 increases production of IL-6 and that as a result, IL-6 and IL-17 are cytokines in the same signaling pathway. As a result, it is alleged that control of IL-17 would be expected to be therapeutic in the treatment of rheumatoid arthritis.

Responding to Applicants' prior argument Carroll *et al.* makes no mention of IL-17 and that Chabaud *et al.*, does not recognize that anti-IL-17 can be effective for treating IL-17 mediated inflammatory disorders, the Examiner argues that Applicants cannot rebut a rejection based on a combination of the references by attacking the references individually.

In response, Applicants first desire to clarify for the record that page 15 of the response filed on December 20, 2001 did indeed address a combined teaching of Carroll *et al.* and Chabaud *et al.*, and that this combined teaching failed to recognize that a common cytokine can treat cartilage damaged from both rheumatoid- and osteo-arthritic causes. As a result, the problem solved by the present invention is distinctly different from that discussed in these references.

Applicants agree that the prior art establishes that IL-17 can induce the production of IL-6, and that anti-IL-6 might be useful to treat rheumatoid arthritis. However, the claimed method relates to the use of anti-IL-17 antibodies for the treatment of cartilage in IL-17 mediated inflammatory disorders, not those mediated by IL-6. As a result, even if IL-17 is an upstream signaling entity from IL-6 in a common cascade of events, a point with which Applicants do not agree, the inhibition of the downstream IL-6 will not necessarily inhibit the same spectrum of disorders as the inhibition of IL-17. The combined teaching of Carroll *et al.* and Chabaud *et al.*

does not teach that the inhibition of IL-17 by an anti-IL-17 is an effective treatment for damaged cartilage.

Chabaud *et al.* is silent about any of the physiological effects of IL-17 inhibition, while Carroll *et al.* discusses the potential impact of anti-IL-6 in the treatment of rheumatoid arthritis.

However, the combined teaching does not teach that anti-IL-17 or even anti-IL-6 antibodies might be useful to treat or prevent further damage to cartilage. As the Examiner is well aware, arthritis is a disease state having a complex pathology. As expressed by Carroll on page 1:

> Synovial inflammation and articular cartilage resorption are complex processes in which inflammatory cells and cells resident in joint tissues contribute. The diverse molecular products of these cells such as cytokines, secreted enzymes, protaglandins, reactive oxygen species and nitric oxide have all been implicated in the promotion of synovial inflammation and joint tissue damage.

The combined teachings of Carroll and Chabaud look at the expression or the attenuation of expression of particular cyokines, however, these references do not show any effect on the attenuation of this expression on the damage or preventing further damage to cartilage. In particular, the combined teaching does not recognize that the attenuation of IL-17 would be effective in specifically treating cartilage (not merely a final disease state) or preventing damage thereto.

In light of the complex pathology of arthritis, even if IL-6 and IL-17 are members of the same signaling pathway, the attenuation of an upstream component will not necessarily have the same result as the attenuation of a downstream component. This differential result is particularly evident when the result being compared between two such components, is not the final disease state (*e.g.*, arthritis), but a mechanistic component thereof (*i.e.*, cartilage destruction).

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3-6, 8, 9, 21, 23-26, 28, 29, 37, 39, 40 and 45 stand rejected under 35 U.S.C. § 103(a).

The Second Rejection under 35 U.S.C. § 103(a)

Claims 1-4, 8-9, 13, 14, 21-26, 28, 29, 33, 34 and 37-39 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kotake *et al., J. Clin. Invest.* 103: 1345-1352 (1999)

and Chabaud *et al.*, *Arthritis & Rheumatism* 42: 963-970 (1999), in view of Carroll *et al.*, *Inflamm. Res.* 47: 1-7 (1998).

In response, the teaching of Chabaud *et al.* and Carroll *et al.* are discussed above. Kotake *et al.* describes that the use of anti-IL-17 antibody to prevent osteoclast formation induced by culture media of synovial tissue extracted from rheumatoid arthritic patients. However, cartilage isn't even mentioned in Kotake *et al.*, much less regimens for the treatment or prevention of the destruction of it. In any event, there is no suggestion or motivation either in Kotake *et al.*, or in a combined teaching of the above three references to use a potential treatment for decreasing bone growth as a treatment for and for preventing further damage to cartilage.

The Third Rejection under 35 U.S.C. § 103(a)

Claims 16 and 18 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chabaud *et al.*, *Arthritis & Rheumatism* 42: 963-970 (1999) and Arend *et al.*, *Ann. Rev. Immunol.* 16: 27-55 (1998).

In response, the cancellation of Claims 16 and 18 renders the rejection moot.

The Fourth Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-9, 21, 23-29, 37, 39, 40, 45 and 46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Troutt (WO 98/23284) in view of Carroll *et al.*, *Inflamm. Research* 47: 1-7 (1998).

The Examiner has alleged that Troutt teaches that IL-17 upregulated release of nitric oxide (NO), which is involved in the pathological conditions of RA and OA, that inhibitors of IL-17 will be useful in regulating levels of NO in OA and that such inhibitors will find therapeutic application in ameliorating the effects of NO in OA, autoimmune and inflammatory diseases.

The Examiner also argues that Carroll teaches that anti-IL-17 antibody can antagonize IL-17 induced production of IL-6.

As a result, the Examiner is essentially arguing the following: Anti-IL-17 can attenuate NO; NO is implicated in both RA and OA, as a result, it is allegedly obvious that anti-IL17 can be used to treat RA and OA.

In response, Applicants draw the Examiner's attention to Example 1D on page 65 of the specification. This example reviews the role of NO in IL-17 induced effects upon cartilage. While it is true that NO is associated with RA and diseased states of cartilage, the jury is still out about whether NO actually causes the cartilage breakdown, is a by-product of the breakdown, or is perhaps associated with an ineffective repair mechanism. Figure 5C shows that the presence of NO actually reduces the cartilage tissue destruction associated with IL-1a and IL-17, and as a result, could actually have an overall beneficial effect.

As the Examiner is well aware, physiology can be quite unpredictable. What might seem to be a reasonable or plausible mechanisms, is often not so, and without the hard experimental data proving the relationship or disproving it, a theory remains just that, a theory.

While Troutt *et al.* does demonstrate that antagonism of IL-17 (through soluble IL-17 R) does attenuation NO production, it does not take the next step of demonstrating or suggesting that attenuation of NO production indeed is effective in treating or preventing further damage to cartilage. What Troutt *et al.* lacks, is not compensated for in Carroll *et al.* Carroll *et al.* only teaches that IL-17 can attenuate the production of IL-6. The combined teaching of these references does not teach or suggest that anti-IL17 antibody might be useful to treat cartilage or prevent further damage to cartilage resulting from a disease state.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3-9, 21, 23-29, 37, 39, 40, 45 and 46 under 35 U.S.C. § 103(a).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding objections and rejections be withdrawn and this case passed to issue.

The examiner is invited to contact the undersigned at (650) 225-1489 in order to expedite the resolution of any remaining issues.

Respectfully submitted,
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Date: June 28, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph at page 1, line 12-15 has been amended as follows:

RELATED APPLICATIONS

The present application claims the benefit of 60/192,103, filed March 24, 2000; and is a continuation-in-part of U.S.S.N. 09/380,142, filed August 25, 1999, which is a 371 of PCT US99/10733 and is a continuation-in-part of U.S.S.N. 09/311,832, filed May 14, ~~2000~~1999, wherein each continuation-in-part further claims benefit of 60/085,679, filed May 15, 1998 and 60/113,621, filed December 23, 1995. ~~The present application also claims the benefit of priority under 35 U.S.C. § 119(e) to U.S.S.N. 60/192,103, filed 24 March 2000~~.

In the claims:

Claims 16-20 have been cancelled.

Claims 9 and 29 have been amended as follows:

1. (Twice amended) A method of treating cartilage in an IL-17 mediated, inflammatory cartilagenous disorder comprising contacting the cartilage with an effective amount of anti-IL-17 antibody.

9. (Twice amended) The method of Claim 8, wherein the ~~antagonist to~~ IL-17 antibody is administered by direct injection into an afflicted cartilagenous region or joint.

29. (Twice amended) The method of Claim 28, wherein the IL-17 ~~antagonist~~ antibody is administered by direct injection into an afflicted cartilagenous region or joint.

37. (Twice amended) A method of treating cartilage in a mammal suffering from an IL-17 mediated, inflammatory cartilagenous disorder, comprising administering to said mammal a therapeutically effective amount of an anti-IL-17 antibody.